DETAILED ACTION

Election/Restrictions

1. This action is in response to a restriction election response filed on June 16, 2008. Applicants have elected Group V without traverse. There are twenty-two claims pending and seven claims under consideration. Claims 2, 9-16, 25, 26 and 34 have been cancelled. Claims 17-24 and 27-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. This is the first action on the merits. The present invention relates to new compounds of formula I, as a free base or a pharmaceutically acceptable salt thereof, to pharmaceutical formulations containing said compounds and to the use of said compounds in therapy. The present invention further relates to a process for the preparation of compounds of formula I and to new intermediates used therein. The restriction requirement is deemed proper and is therefore made FINAL.

Priority

3. Acknowledgment is made of Applicant's claim for foreign priority. This application 10/539,545, filed June 16, 2005, is a national stage application of PCT/SE03/01957, filed December 15, 2003, which claims foreign priority to Swedish Application No. 0203753-9, filed December 17, 2002.

Specification

4. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any of the errors of which applicant may become aware of in the specification.

Claim Objections

5. Claim 1 is objected to because of the following informalities:

Claim 1 is objected to for containing superfluous material with the claim. Claim 1 contains a term $(R^3)_m$ in which the "m" term may only equal 0 (m=0). Therefore the entire R^3 term is unnecessary and can be deleted from the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 1 and 3-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound, composition, or pharmaceutically acceptable salt, where Y is a $CONR^5$ group and R represents either a 4-methyl-piperazinylsulfonyl group or a 4-pyrrolidin-1-ylsulfonyl group, does not reasonably provide enablement for a solvate or solvate of a salt thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

9. The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation. (*United States v. Teletronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See *Ex parte*

Forman 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

1) *Amount of guidance provided by Applicant.* Applicant has provided no guidance, examples, or provided any chemical or biological data and/or testing results of any compounds or compositions with R groups other than those previously mentioned or any compounds or compositions which are solvates or solvates of salts in the current application.

The Applicant has demonstrated within the application how to make a select number of pyrazine compounds and compositions, however, applicant has not demonstrated any of the thousands of potential other compounds or compositions that could potentially exist as solvates or solvates of salts.

2) Unpredictability in the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. (USPQ 18, 24 (CCPA 1970). See *In re Fisher*, 427 F.2d 833, 839, 166.

Chemistry is unpredictable. See In Re Marzocchi and Horton 169 USPQ at 367 paragraph 3:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of

> structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work .....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious)." Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

The scope of "solvate" or "solvate of a salt" is not adequately enabled or defined. Applicants provide no guidance as how the compounds are made more active *in vivo*. Solvates cannot be predicted and therefore are not capable of being claimed if the applicant cannot properly enable a particular solvate.

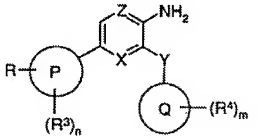
> "Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds. Certain molecular shapes and features favor the formation of crystals without solvent; these compounds tend to be stabilized by efficient packing of molecules in the crystal lattice, whereas other crystal forms are more stable in the presence of water and/or solvents. There may be too many possibilities so that no computer programs are currently available for predicting the crystal structures of hydrates and solvates. Vippagunta et. al. Advanced Drug Delivery Reviews 48 (2001) 3-26.

3) *Number of working examples.* The compound core depicted with specific substituents represent a narrow subgenus for which applicant has provided sufficient guidance to make and use; however, this disclosure is not sufficient to allow extrapolation of the limited examples to enable the scope of the compounds instantly claimed. Applicant has provided no working examples of any compounds, compositions

or salts other than those previously mentioned or any compounds or compositions which are solvates or solvates of salts.

Within the specification, "specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. *Markush* claims must be provided with support in the disclosure for each member of the *Markush* group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula." See MPEP 608.01(p).

4) *Scope of the claims.* The scope of the claims involves all of the thousands of compounds of Formula (I) of claim 1 with the following general formula:



Where X and Z are N and P is a phenyl ring, thus the scope of the claims is broad.

5) *Nature of the invention.* The present invention relates to new compounds of formula I, as a free base or a pharmaceutically acceptable salt thereof, to pharmaceutical formulations containing said compounds and to the use of said compounds in therapy. The present invention further relates to a process for the preparation of compounds of formula I and to new intermediates used therein.

6) *Level of skill in the art.* The artisan using Applicants invention would be a chemist with a M.S. or Ph.D. degree, and having several years of bench experience.

MPEP §2164.01 (a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here that Applicant is not enabled for treating the disease mentioned.

Claim Rejections - 35 USC § 112, 2nd paragraph

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1, 3-6 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The scope of "heteroaryl" and "heterocyclic ring" requires clarification since applicants' examples in the specification are not limited but are merely various examples which only cover a minute number of potential results. See definitions on p. 20 of the specification. Where applicants define terms with a special meaning, they must set out the special definition with "reasonable clarity, deliberateness and precision". Note *Teleflex v. Ficosa*, 63 USPQ2d 1374; Rexnord Corp v. Laitram Corp. 60 USPQ2d 1851 and MPEP 2111.01.

In the absence of the specific moieties intended to effect modification by "substitution" or attachment to the chemical core claimed, the term " optionally substituted" renders the claim in which it appears indefinite in all occurrences wherein applicant fails to articulate by chemical name, structural formula or sufficiently distinct functional language, the particular moieties applicant regards as those which will facilitate substitution, requisite to identifying the composition of matter claimed.

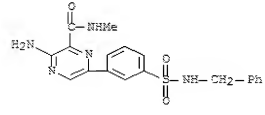
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 5 and 8 are rejected under 35 U.S.C. 102(e) as being anticipated by Buhr, et. al. WO2003093297. The prior art describes the following compound:

RN 625462-23-7 CAPLUS
CN 2-Pyrazinecarboxamide, 3-amino-N-methyl-6-[3-[[(phenylmethyl)amino]sulfonyl]phenyl]- (CA INDEX NAME)



Where X and Z are N; Y is a C(=O)N; Q is a CH_3; n=0; P is a phenyl ring; R is $SO_2NR^1R^2$ where R^1 is a H and R^2 is a alkylphenyl group.

Conclusion

16. Claims 1 and 3-8 are rejected.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey H. Murray whose telephone number is (571) 272-9023. The examiner can normally be reached on Mon.-Thurs. 7:30-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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